

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 December 2000 (21.12.2000)

PCT

(10) International Publication Number
WO 00/76488 A2

(51) International Patent Classification⁷: **A61K 31/00**

(21) International Application Number: **PCT/GB00/02330**

(22) International Filing Date: **14 June 2000 (14.06.2000)**

(25) Filing Language: **English**

(26) Publication Language: **English**

(30) Priority Data:
9913782.0 14 June 1999 (14.06.1999) GB

(71) Applicant (*for all designated States except US*):
SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventor; and

(75) Inventor/Applicant (*for US only*): **NATHWANI, Ameet [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).**

(74) Agent: **RUTTER, Keith; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).**

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/76488 A2

(54) Title: **NOVEL TREATMENT**

(57) Abstract: A method for delaying or preventing the onset of Type 1 diabetes in a human or non-human mammal, which method comprises the administration of an effective, non-toxic and pharmaceutically acceptable amount of a PPAR agonist, such Compound (I), or a pharmaceutically acceptable derivative thereof, to the patient in need thereof.

NOVEL TREATMENT

This invention relates to a novel treatment and in particular to a method for delaying or preventing the onset of Type 1 diabetes.

Type 1 diabetes or insulin dependant diabetes has an auto-immune basis and usually develops in childhood or early adulthood. Persons who have a predisposition to developing type 1 diabetes mellitus can be identified by the presence of specific autoantibodies to glutamate decarboxylase (GAD). The onset of symptoms is often related to milestones in child development such as puberty which is associated with an increase in insulin resistance due to the elevated levels of circulating anabolic hormones. This, in turn, is believed to accelerate the rate of the auto-immune destruction of the insulin producing beta-cells and bring about the onset of clinical diabetes. It is believed that reducing the stress produced on the pancreatic beta-cell at these critical periods of increased insulin resistance will delay or prevent the onset of Type 1 diabetes.

Insulin resistance is considered to accelerate the utilisation of depleted insulin stores. This heightened insulin utilisation may accelerate the autoimmune destruction of the beta-cells. Reducing the burden of this insulin requirement may thereby slow the progression of insulin depletion and hence the onset of Type 1 diabetes.

European Patent Application, Publication Number 0306228 discloses certain thiazolidinedione derivatives which are disclosed *inter alia* as having hypoglycaemic and hypolipidaemic activity and activity in treating certain eating disorders. The compound of example 30 of EP 0306228 is 5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione (or 'Compound (I)').

European Patent Applications, Publication Numbers: 0306228, 0008203, 0139421, 0032128, 0428312, 0489663, 0155845, 0257781, 0208420, 0177353, 0319189, 0332331, 0332332, 0528734, 0508740; International Patent Application, Publication Numbers 92/18501, 93/02079, 93/22445 and United States Patent Numbers 5104888 and 5478852, also disclose certain thiazolidinedione derivatives which are stated to have hypoglycaemic and hypolipidaemic activity.

It is known that the γ -isoform of peroxisome proliferator-activated receptor (herein after PPAR γ) is member of a nuclear receptor superfamily that includes receptors for the steroid, thyroid and retinoid hormones (Evans, Science 240, 889-895, (1988)). It is also known from Chawla *et al* that PPAR γ is expressed early during the differentiation of adipocytes (Endocrinology 135,798-800, 1994).

It is known from J. Biol. Chem., 270,12963-12966 that thiazolidinediones such as Compound (I) are PPAR γ agonists.

It is known that troglitazone and pioglitazone can prevent the development of Type 1 diabetes but only that induced by multiple low-dose streptozotocin in mice
5 (Life Sciences, 1999, 65, 12, 1287-1296; Diabetes Research and Clinical Practice 1999, 44, 2 107-114).

It is now considered that individuals who are at risk from the development of Type 1 diabetes due to increasing insulin resistance, especially during puberty, can be treated with a PPAR γ agonist so as to delay or prevent the onset of Type 1 diabetes.

10 Accordingly, the invention provides a method for delaying or preventing the onset of Type 1 diabetes, especially by reducing insulin resistance, in a human or non-human mammal, which method comprises the administration of an effective, non-toxic and pharmaceutically acceptable amount of a PPAR agonist, such as Compound (I), or a pharmaceutically acceptable derivative thereof, to the patient in
15 need thereof.

In particular the invention provides a method for delaying or preventing the onset of Type 1 diabetes by reducing the insulin resistance associated with puberty.

In an alternative aspect, the invention provides a method for delaying or preventing the onset of Type 1 diabetes in a human having an elevated level of
20 antibodies to GAD, which method comprises the administration of an effective, non-toxic and pharmaceutically acceptable amount of a PPAR agonist, such as Compound (I), or a pharmaceutically acceptable derivative thereof, to the patient in need thereof.

In particular, there is provided a method for delaying or preventing the onset of Type 1 diabetes in a pre-pubescent human having an elevated level of antibodies
25 to GAD.

In yet a further aspect of the invention, there is provided a method for delaying or preventing the onset of Type 1 diabetes in a pre-pubescent human which method comprises the administration of an effective, non-toxic and pharmaceutically acceptable amount of a PPAR agonist, such as Compound (I), or a pharmaceutically
30 acceptable derivative thereof, to the patient in need thereof.

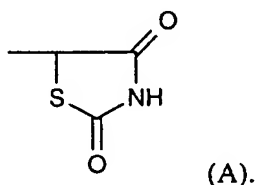
The present invention is also considered to provide a method for slowing the progression of insulin depletion in a Type 1 diabetic or a person having a disposition to Type 1 diabetes, which method comprises the administration of an effective, non-toxic and pharmaceutically acceptable amount of a PPAR agonist, such as Compound
35 (I), or a pharmaceutically acceptable derivative thereof, to the patient in need thereof.

Suitably, the treatments disclosed herein delay the onset of Type 1 diabetes.

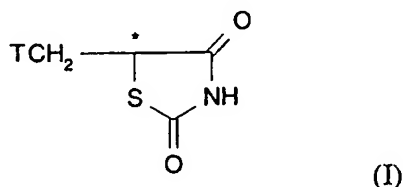
Suitably, the treatments disclosed herein prevent the onset of Type 1 diabetes.

Persons having a disposition to Type 1 diabetes include those having an elevated level of antibodies to GAD.

- 5 Suitable PPAR γ agonists include thiazolidinediones, especially thiazolidine-2,4-diones, that is a compound comprising a moiety of formula (A):



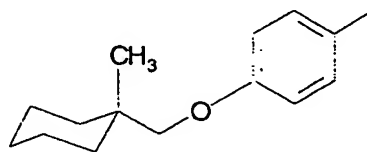
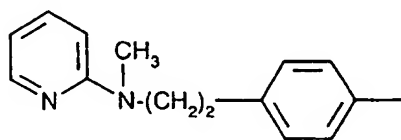
- 10 Suitable compounds comprising a moiety of formula (a) include compounds of formula (I):

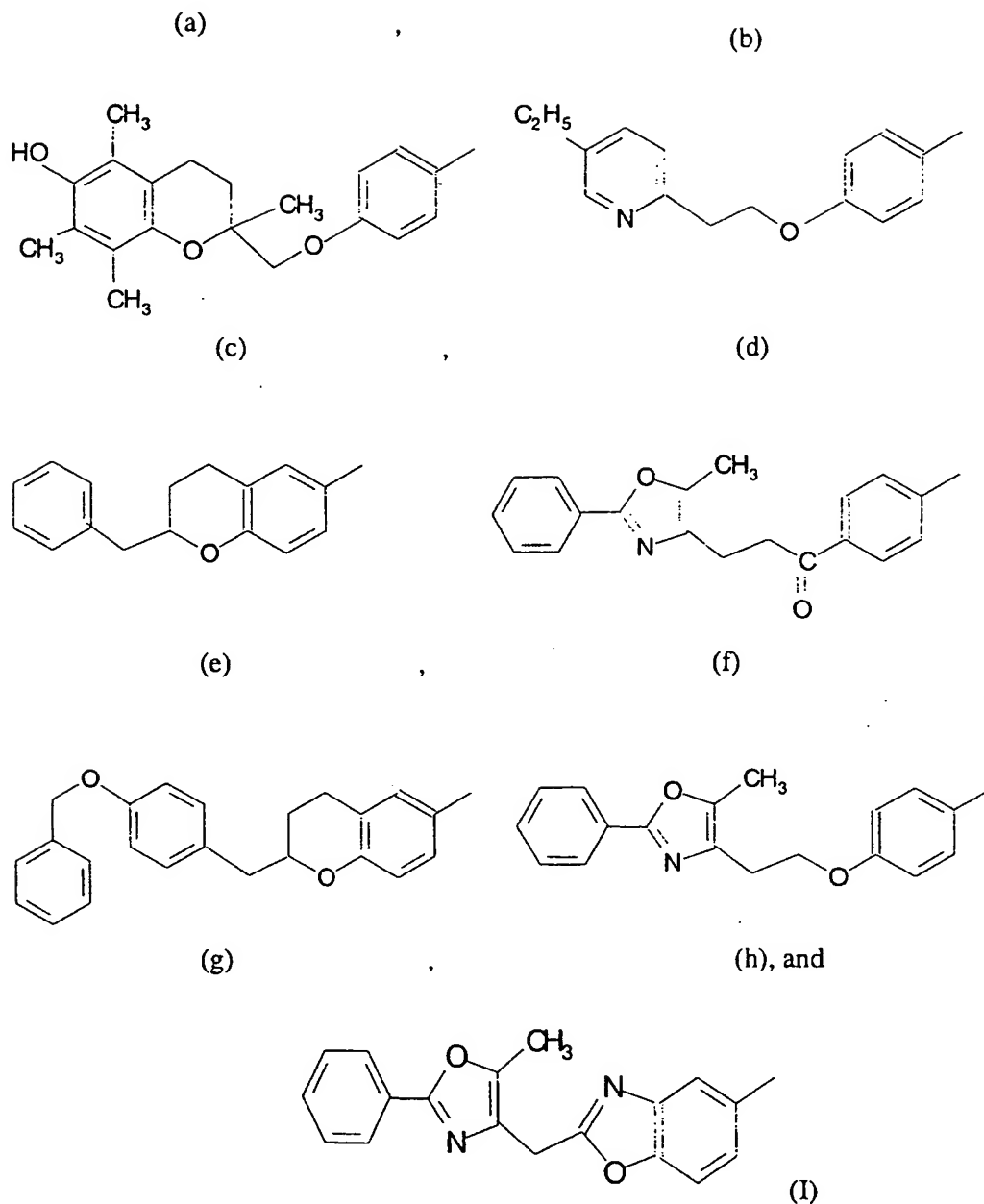


- 15 or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, wherein T represents an aryl or heterocyclyl group optionally substituted with one or more alkyl groups, aralkyl groups or heterocyclylalkyl groups, the said alkyl, aralkyl and heterocyclylalkyl groups themselves being optionally substituted.

- 20 Suitably, the carbon atom marked with an asterisk (*) in formula (I) is a chiral carbon.

In particular T represents a moiety selected from the list consisting of (a), (b), (c), (d), (e), (f), (g), (h) and (i):





In particular should be mentioned the moieties of formula (a), (b), (c), (d) and (e).

10

Also included in the treatment of the invention are the PPAR γ agonists disclosed in European Patent Applications, Publication Numbers: 0306228, 0008203, 0139421, 0032128, 0428312, 0489663, 0155845, 0257781, 0208420, 0177353,

0319189, 0332331, 0332332, 0528734 and 0508740, International Patent Application, Publication Numbers 92/18501, 93/02079, 93/22445 and United States Patent Numbers 5104888 and 5478852, especially the specific example thereof. The contents of these publications are included herein by reference.

- 5 Thiazolidinedione PPAR γ agonists may exist in one of several tautomeric forms, all of which are encompassed by the present invention as individual tautomeric forms or as mixtures thereof. Where a PPAR γ agonist contains a chiral carbon, and hence exists in one or more stereoisomeric forms or where one or more geometric isomers exist, it will be appreciated that the method of the present
10 invention encompasses all of the said forms of the PPAR γ agonists whether as individual isomers or as mixtures of isomers, including racemates.

Particular examples of thiazolidinediones are those disclosed in EP 0306228 and WO94/05659. Further particular examples are the thiazolidinediones disclosed in EP0139421 and USP 5478852.

- 15 A preferred thiazolidinedione is Compound (I).

- Further particular thiazolidinediones are, (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]benzyl]thiazolidine-2,4-dione (or ciglitazone), 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl]thiazolidine-2,4-dione (or englitazone), or, especially, 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone).
20

A particular thiazolidinediones is 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone).

- When used herein the term 'PPAR γ agonist' relates to an agonist, such as a
25 small molecular weight agonist, of the peroxisomal proliferator-activated receptor of the gamma subtype, this nuclear receptor is a member of the ligand activated transcription factor family that include the steroid, retinoid and thyroid receptors.

PPAR γ agonist activity may be assessed by use of the methodology disclosed by Lehmann et al : Journal of Biological Chem., 270, 12953-12956 (1995).

- 30 When used herein the term 'aryl' includes phenyl and naphthyl optionally substituted with up to five, preferably up to three, groups selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxy, amino, nitro, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

- Suitable heterocyclyl groups are aromatic and non-aromatic heterocyclic
35 groups.

Suitable non-aromatic heterocyclic groups include groups comprising single or fused ring heterocyclic groups comprising up to 4 hetero atoms in each ring selected from oxygen, sulphur or nitrogen, optionally fused to one or more aryl groups.

Suitable aromatic heterocyclyl groups include substituted or unsubstituted, single or fused ring aromatic heterocyclyl groups comprising up to 4 hetero atoms in each ring selected from oxygen, sulphur or nitrogen.

Favoured aromatic heterocyclyl groups include substituted or unsubstituted single ring aromatic heterocyclyl groups having 5 to 7 ring atoms, preferably 5 or 6 ring atoms.

In particular, the aromatic heterocyclyl groups comprise 1, 2 or 3 heteroatoms, especially 1 or 2, selected from oxygen, sulphur or nitrogen.

Suitable substituents for the heterocyclyl include up to 4 substituents selected from the group consisting of: alkyl, alkoxy, aryl and halogen or any two substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a benzene ring, and wherein the carbon atoms of the aryl group represented by the said two substituents may themselves be substituted or unsubstituted.

It will be appreciated that where the above mentioned definitions of 'aryl', 'heterocyclyl' and the substituents thereof differ from those in the above mentioned patent publications with respect to the particular compounds disclosed therein, that the definitions in the said publications prevail.

When used herein the term 'halogen' refers to fluorine, chlorine, bromine and iodine; preferably chlorine.

When used herein the terms 'alkyl' and 'alkoxy' relate to groups having straight or branched carbon chains, containing up to 12 carbon atoms.

When used herein the term 'acyl' includes alkylcarbonyl groups.

Suitable alkyl groups are C₁₋₁₂ alkyl groups, especially C₁₋₆ alkyl groups e.g. methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl or tert-butyl groups.

Suitable substituents for any alkyl group include those indicated above in relation to the term "aryl".

Suitable derivatives of a PPAR γ agonist are pharmaceutically acceptable derivatives, for example salts and solvates.

Suitable derivatives of any particular PPAR γ agonist include those disclosed in the above mentioned publications.

Suitable pharmaceutically acceptable salts include salts of salts derived from appropriate acids, such as acid addition salts, or bases.

Suitable pharmaceutically acceptable salts include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-b-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

Suitable acid addition salts include pharmaceutically acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and pharmaceutically acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methane-sulphonate, α -keto glutarate and α -glycerophosphate, especially the maleate salt.

Suitable pharmaceutically acceptable salts of Compound (I) are as disclosed in EP 0306228 and WO94/05659 and include maleate salts.

Suitable pharmaceutically acceptable solvates include hydrates.

Suitable pharmaceutically acceptable solvates of Compound (I) are as disclosed in EP 0306228 and WO94/05659 and include hydrates.

The PPAR γ agonists, such as the thiazolidinediones, referred to herein are conveniently prepared according to the methods disclosed in the above mentioned patent publications in which they are disclosed: Thus Compound (I), or the tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, may be prepared using the processes described in EP 0306228 and WO94/05659.

The salts and/or solvates of the thiazolidinediones may be prepared and isolated according to conventional procedures for example those disclosed in the above mentioned, patent publications.

The present invention also provides a PPAR γ agonist or a pharmaceutically acceptable derivative thereof, for use in a method for delaying or preventing the onset of Type 1 diabetes, especially by reducing insulin resistance.

In an alternative aspect, the invention provides a PPAR γ agonist or a pharmaceutically acceptable derivative thereof, for use in a method for delaying or

preventing the onset of Type 1 diabetes in a human having an elevated level of antibodies to GAD.

In yet a further aspect of the invention, there is provided a PPAR γ agonist or a pharmaceutically acceptable derivative thereof, for use in a method for delaying or preventing the onset of Type 1 diabetes in a pre-pubescent human.

The present invention is also considered to provide a PPAR γ agonist or a pharmaceutically acceptable derivative thereof, for use in a method for slowing the progression of insulin depletion in a Type 1 diabetic or a pre-Type 1 diabetic.

The present invention also provides a PPAR γ agonist or a pharmaceutically acceptable derivative thereof, for use in the manufacture of a medicament for: delaying or preventing the onset of Type 1 diabetes, especially by reducing insulin resistance; delaying or preventing the onset of Type 1 diabetes in a human having an elevated level of antibodies to GAD; delaying or preventing the onset of Type 1 diabetes in a pre-pubescent human; or for slowing the progression of insulin depletion in a Type 1 diabetic or a pre-Type 1 diabetic.

In the above mentioned treatment methods the PPAR γ agonist, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

In the treatments of the invention, the PPAR γ agonist mentioned herein is formulated and administered in accordance with the methods disclosed in the above mentioned patent applications and patents.

Accordingly, the present invention also provides a pharmaceutical composition for delaying or preventing the onset of Type 1 diabetes, especially by reducing insulin resistance; delaying or preventing the onset of Type 1 diabetes in a human having an elevated level of antibodies to GAD; delaying or preventing the onset of Type 1 diabetes in a pre-pubescent human; or slowing the progression of insulin depletion in a Type 1 diabetic or a pre-Type 1 diabetic, which composition comprises a PPAR γ agonist, or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier therefor.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

Usually the pharmaceutical compositions of the present invention will be adapted for oral administration, although compositions for administration by other routes, such as by injection and percutaneous absorption are also envisaged.

Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules. Other fixed unit dosage forms, such as powders presented in sachets, may also be used.

In accordance with conventional pharmaceutical practice the carrier may comprise a diluent, filler, disintegrant, wetting agent, lubricant, colourant, flavourant or other conventional adjuvant.

Typical carriers include, for example, microcrystalline cellulose, starch, sodium starch glycollate, polyvinylpyrrolidone, polyvinylpolypyrrolidone, magnesium stearate, sodium lauryl sulphate or sucrose.

Suitable dosages of the PPAR γ agonist include the known doses for these compounds as described or referred to in reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Complete Drug Reference (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) or the above mentioned publications or doses which can be determined by standard procedures.

Suitable dosages of the Compound (I) include those disclosed in EP 0306228 and WO94/05659 and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound (I).

Particular dosages of Compound (I) are 2mg, 4mg and 8mg.

Particular dosages of troglitazone include from 100 to 800mg such as 200, 400, 600 or 800mg.

Particular dosages of pioglitazone include from 5 to 50mg, including 10 to 40mg, such as 15, 20, 30 or 40 mg of pioglitazone.

The composition of the invention may be administered from 1 to 6 times a day, but most preferably 1 or 2 times per day.

The solid oral compositions may be prepared by conventional methods of blending, filling or tableting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate
5 gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl
10 p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound
15 can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially
20 the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

25 Compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending upon the method of administration.

Compositions may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

30 The compositions are formulated according to conventional methods, such as those disclosed in standard reference texts, for example the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Complete Drug Reference (London, The Pharmaceutical Press) and Harry's Cosmeticology (Leonard Hill Books).

The activity of compounds in the treatment of the present invention can be determined using known methodology, for example by use of animal models such as the BB rat or NOD mouse using procedures disclosed by Tochino Y (1987) the NOD mouse as a model of Type 1 diabetes CRC Critical reviews Immunology 8, 49-81 or
5 Baekkesskov S et al 1984 Autoantibodies to a 64 kD islet cell protein precede the onset of spontaneous diabetes in the BB rat. Science 224, 1348-1350.

As indicated above the treatment is effective in patients who have elevated levels of antibodies to GAD and are therefore predisposed to the development of Type 1 diabetes, especially during periods of increased insulin resistance (for
10 example at puberty). The methodology for determining elevated levels of antibodies to GAD are those used conventionally in the art, for example those disclosed by W A Hagopian *et al* in J Clin. Invest., Vol 95, 1995, 1505-1511.

No adverse toxicological effects are expected for the compositions or methods of the invention in the above mentioned dosage ranges.

15

Claims:

1. A method for delaying or preventing the onset of Type 1 diabetes in a human or non-human mammal, which method comprises the administration of an effective,
5 non-toxic and pharmaceutically acceptable amount of a PPAR agonist, such as Compound (I), or a pharmaceutically acceptable derivative thereof, to the patient in need thereof.
2. A method according to claim 1, wherein the delay or prevention of onset of
10 Type 1 diabetes is provided by reducing insulin resistance.
3. A method according to claim 1, wherein the delay or prevention in onset of Type 1 diabetes is provided by reducing the insulin resistance associated with
15 puberty.
4. A method for delaying or preventing the onset of Type 1 diabetes in a human having an elevated level of antibodies to GAD, which method comprises the administration of an effective, non-toxic and pharmaceutically acceptable amount of
20 a PPAR agonist, such as Compound (I), or a pharmaceutically acceptable derivative thereof, to the patient in need thereof.
5. A method according to claim 4, wherein the human is a pre-pubescent human having an elevated level of antibodies to GAD.
- 25 6. A method for delaying or preventing the onset of Type 1 diabetes in a pre-pubescent human which method comprises the administration of an effective, non-toxic and pharmaceutically acceptable amount of a PPAR agonist, such as Compound (I), or a pharmaceutically acceptable derivative thereof, to the patient in need thereof.
- 30 7. A method for slowing the progression of insulin depletion in a Type 1 diabetic or a pre-Type 1 diabetic which method comprises the administration of an effective, non-toxic and pharmaceutically acceptable amount of a PPAR agonist, such as Compound (I), or a pharmaceutically acceptable derivative thereof, to the
35 patient in need thereof.

8. A method according to claim 1, 4, 6 or 7 wherein the PPAR agonist is a thiazolidinedione.
- 5 9. A method according to claim 8, wherein the PPAR agonist is selected from the list consisting of: Compound (I), (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]benzyl] thiazolidine-2,4-dione (or ciglitazone), 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl]thiazolidine-2,4-
- 10 dione (or englitazone), and 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone).
10. A method according to claim 8, wherein the PPAR agonist is Compound (I).
- 15 11. A method according to claim 8, wherein the PPAR agonist is 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone).

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 December 2000 (21.12.2000)

PCT

(10) International Publication Number
WO 00/76488 A3

- (51) International Patent Classification⁷: A61K 31/00, 31/427, 31/426, 31/4439, A61P 3/10
- (21) International Application Number: PCT/GB00/02330
- (22) International Filing Date: 14 June 2000 (14.06.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
9913782.0 14 June 1999 (14.06.1999) GB
- (71) Applicant (for all designated States except US):
SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): NATHWANI, Ameet [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).
- (74) Agent: RUTTER, Keith; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— With international search report.
- (88) Date of publication of the international search report:
10 May 2001
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF A PPAR AGONIST FOR TREATING TYPE 1 DIABETES

(57) Abstract: A method for delaying or preventing the onset of Type 1 diabetes in a human or non-human mammal, which method comprises the administration of an effective, non-toxic and pharmaceutically acceptable amount of a PPAR agonist, such as, (+)-5-''4-' (3,4-dihydro- 6-hydroxy- 2,5,7,8-tetramethyl- 2H-1-benzopyran- 2-yl)methoxy!phenyl!!Menthyl!!-2,4- thiazolidinedione (or troglitazone), 5-''4-' (1-methylcyclohexylmethoxy! benzyl! thiazolidine-2, 4-dione (or ciglitazone), 5-''(2-benzyl-2,3-dihydrobenzopyran)- 5-ylmethyl) thiazolidine-2,4-dione (or englitazone), and 5-''4-'2 -(5-ethylpyridin- 2-yl)ethoxy! benzyl! thiazolidine-2,4- dione, or pioglitazone, or a pharmaceutically acceptable derivative thereof, to the patient in need thereof.

WO 00/76488 A3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/02330

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/00 A61K31/427 A61K31/426 A61K31/4439 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, EMBASE, CHEM ABS Data, BIOSIS, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 62766 A (MACPHEE COLIN HOUSTON ;SMITHKLINE BEECHAM PLC (GB)) 26 October 2000 (2000-10-26) abstract page 3, line 14 - line 17 page 4, line 14 - line 20; claims 1,7,10,11	1-11
P,X	OGAWA J ET AL: "Troglitazone can prevent development of type 1 diabetes induced by multiple low-dose streptozotocin in mice." LIFE SCIENCES, (1999) 65 (12) 1287-96. , XP000978446 cited in the application the whole document	1-9

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

11 January 2001

Date of mailing of the international search report

05/02/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hoff, P

INTERNATIONAL SEARCH REPORT

Intern al Application No

PCT/GB 00/02330

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 45141 A (FUKUSHIGE JUNICHIRO ;HORIKOSHI HIROYOSHI (JP); HOSOKAWA TSUNEMICHI) 4 December 1997 (1997-12-04) & EP 0 953 355 A (SANKYO COMPANY) 3 November 1999 (1999-11-03) page 3, line 16 - line 57; examples 1,3,4 ----	1-11
X	TOMINAGA, MAKOTO (1) ET AL: "Effect of thiazolidinediones on insulin resistance of non- insulin -dependent and insulin -dependent diabetes mellitus model rats." YAMAGATA MEDICAL JOURNAL, (1997) VOL. 15, NO. 1, PP. 35-43. , XP000978587 the whole document ----	1-9,11
X	TOMINAGA M ET AL: "Thiazolidinediones (AD - 4833 and CS - 045) improve hepatic insulin resistance in streptozotocin-induced diabetic rats." ENDOCRINE JOURNAL, (1993 JUN) 40 (3) 343-9. , XP000978449 the whole document ----	1-9,11
X	BEALES P E ET AL: "Troglitazone prevents insulin dependent diabetes in the non-obese diabetic mouse." EUROPEAN JOURNAL OF PHARMACOLOGY, (1998 SEP 18) 357 (2-3) 221-5. , XP000978448 the whole document ----	1-9
X	TAKAMURA T ET AL: "Pioglitazone prevents mice from multiple low-dose streptozotocin-induced insulinitis and diabetes." DIABETES RESEARCH AND CLINICAL PRACTICE, (1999 MAY) 44 (2) 107-14. , XP000978465 cited in the application the whole document ----	1-9,11
X	FUKUDA M. ET AL: "CS - 045, a new oral antidiabetic agent, prevents the development of cyclophosphamide-induced diabetes in NOD mice." JOURNAL OF THE JAPAN DIABETES SOCIETY, (1994) 37/2 (127-130). , XP000978444 abstract ----- -/--	1-9

INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/GB 00/02330

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FUJIWARA, T. ET AL: "Suppressive effect of troglitazone on development of type 1 diabetes induced by multiple low-dose streptozotocin injection in mice." DIABETOLOGIA, (1997) VOL. 40, NO. SUPPL. 1, PP. A311. MEETING INFO.: 16TH INTERNATIONAL DIABETES FEDERATION CONGRESS HELSINKI, FINLAND JULY 20-25, 1997 , XP000978468 abstract ---	1-9
X	FUKUDA, MASAHIRO ET AL: "Antioxidants can prevent the development of type I diabetes in NOD mice" INT. CONGR. SER. (1995), 1100(DIABETES 1994), 1083-6 , XP000978441 the whole document ---	1-9
X	WO 97 43283 A (BOEHRINGER MANNHEIM GMBH ;WOLFF HANS PETER (DE); WITTE ERNST CHRIS) 20 November 1997 (1997-11-20) abstract page 1, line 1 - line 16 ---	1-9
X	LESLIE R.D.G. ET AL: "The role of insulin resistance in the natural history of Type 1 diabetes." DIABETIC MEDICINE, (1997) 14/4 (327-331). XP000978464 the whole document ---	1-9
X	WO 97 31907 A (GLAXO GROUP LTD ;WILLSON TIMOTHY MARK (US); MOOK ROBERT ANTHONY JR) 4 September 1997 (1997-09-04) abstract; claims 1,24-26 ---	1-7
A	SMISMANS, ANNICK ET AL: "Damaged rat beta cells discharge glutamate decarboxylase in the extracellular medium." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1996) VOL. 228, NO. 2, PP. 293-297. , XP000971968 the whole document ---	4,5
A	"THE MERCK MANUAL" 1999 , MERCK RESEARCH LABORATORIES XP002157021 page 165 -page 177 --- -/--	3-6

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/02330

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>EP 0 306 228 A (BEECHAM GROUP PLC) 8 March 1989 (1989-03-08) cited in the application abstract; claims; examples</p>	1-11

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-7 relate to a compound defined by reference to a desirable characteristic or property, namely "PPAR agonist".

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to its pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Furthermore, present claim 8 relates to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds mentioned in claims 9-11, with due regard to the general idea underlying the present invention.

Claims searched completely: 9-11
Claims searched incompletely: 1-8

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/02330

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0062766	A	26-10-2000	NONE	
WO 9745141	A	04-12-1997	AU 710249 B	16-09-1999
			AU 2976597 A	05-01-1998
			CA 2257284 A	04-12-1997
			CN 1226833 A	25-08-1999
			CZ 9803885 A	14-07-1999
			EP 0953355 A	03-11-1999
			HU 9903292 A	28-07-2000
			JP 10212247 A	11-08-1998
			NO 985571 A	27-01-1999
			US 6150371 A	21-11-2000
WO 9743283	A	20-11-1997	AU 3091197 A	05-12-1997
WO 9731907	A	04-09-1997	AP 780 A	22-11-1999
			AU 717699 B	30-03-2000
			AU 2093597 A	16-09-1997
			BG 102792 A	31-08-1999
			BR 9707786 A	27-07-1999
			CA 2247443 A	04-09-1997
			CN 1218460 A	02-06-1999
			CZ 9802750 A	13-01-1999
			EP 0888317 A	07-01-1999
			HR 970110 A	30-04-1998
			JP 2000507216 T	13-06-2000
			NO 983940 A	27-10-1998
			PL 328871 A	01-03-1999
			SK 116398 A	13-04-1999
EP 0306228	A	08-03-1989	AT 186724 T	15-12-1999
			AU 2173888 A	09-03-1989
			BR 1100841 A	20-06-2000
			CA 1328452 A	12-04-1994
			CA 1339902 A	09-06-1998
			CZ 9103916 A	17-03-1993
			DE 3856378 D	23-12-1999
			DE 3856378 T	11-05-2000
			DK 490288 A	05-03-1989
			EP 0842925 A	20-05-1998
			ES 2137915 T	01-01-2000
			GR 3031873 T	29-02-2000
			JP 10194970 A	28-07-1998
			JP 10194971 A	28-07-1998
			JP 1131169 A	24-05-1989
			JP 2614497 B	28-05-1997
			JP 2817840 B	30-10-1998
			JP 9183771 A	15-07-1997
			JP 2837139 B	14-12-1998
			JP 9183726 A	15-07-1997
			JP 9183772 A	15-07-1997
			KR 164207 B	15-01-1999
			KR 164275 B	15-01-1999
			KR 169463 B	15-01-1999
			NZ 226027 A	26-03-1992
			PT 88410 A, B	31-07-1989
			SG 59988 A	22-02-1999
			US 5646169 A	08-07-1997

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 00/02330

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0306228 A		US 5002953 A	26-03-1991
		US 5521201 A	28-05-1996
		US 5232925 A	03-08-1993
		US 5194443 A	16-03-1993
		US 5756525 A	26-05-1998
		US 5260445 A	09-11-1993
		ZA 8806536 A	26-07-1989
<hr/>			